Editorial

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Chronic hepatitis C genotype 2 and 3: Are we ready for personalized medicine?

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Over the last several years, efforts have been made in patients with genotypes 2 and 3 chronic hepatitis C (CHC) to assess whether shortening the duration of therapy with pegylated interferon (PEG-IFN) and ribavirin (RBV) might preserve the efficacy of the standard 24 week treatment duration while decreasing side-effects and improving tolerability. Data on viral kinetics have shown that both the effectiveness of IFN in blocking production of the virus in the first phase of viral decline (rapid decline) and the rate of decline in the second phase (slower decline) differ in patients with hepatitis C virus (HCV) genotype 1 and in those with genotypes 2 or 3 [1,2]. This led several investigators to the hypothesis that in patients with CHC genotype 2 or 3 and rapid virologic response (RVR, i.e. HCV RNA undetectable after 4 weeks of therapy), 12–16 weeks of treatment with PEG-IFN and RBV may be as effective as a course of 24 weeks [3,4], which induces sustained virologic response (SVR) in about 80% of patients [5,6].

While several European studies [3,7–9] and a study from Taiwan [10] appeared to support this hypothesis, the results were somewhat different in the ACCELERATE [11] and NORTH-C [12] trials. The conflicting results may have been due to differences in the study design, prevalence of advanced fibrosis and cirrhosis, baseline viral counts, predominant genotype, ethnic background of the study population, and different RBV dosing schedules. The earlier trials by Dalgard *et al.* [7] and VonWagner *et al.* [8] included a relatively young HCV population with mostly early-stage fibrosis, while almost 25% of patients in ACCELERATE (a large prospective randomized, multinational non-inferiority trial) had bridging fibrosis or cirrhosis [11]. The absence of bridging fibrosis/cirrhosis was shown to be an independent predictor of SVR among genotype 2 and 3 patients by both Dalgard *et al.* [7] and Shiffman *et al.* [11], although this has not been reported by others [3,8,13].

Unlike most prior studies which evaluated truncation of treatment duration to less than 24 weeks in genotype 2 and 3 patients, ACCELERATE used a fixed dose RBV (800 mg/d). Since the mean body weight of ACCELERATE patients with genotype 2, for example, was about 84 kg [11], that resulted in a mean daily dose of RBV of 9.52 mg/kg, in contrast to 15.3 mg/kg in the study of genotype 2 patients by Yu *et al.* (mean body weight about 66 kg) [10]. Although Hadziyannis *et al.* [14] previously showed that a combination of PEG-IFN alfa-2a and RBV 800 mg/d was as effective as a combination of PEG-IFN alfa-2a and RBV 1000–1200 mg/d in patients with genotypes 2 and 3 using a 24-week treatment regimen, the prevailing literature as of the publication of the ACCELERATE study left open the question of whether a higher weight-based dose of RBV might still permit a shorter-duration of treatment of genotype 2 and 3 patients with RVR without increasing the risk of relapse.

The notion that the impairment in SVR with truncated therapy in RVR patients in ACCELERATE was due to the low, flat RBV dose (800 mg daily) used in that study was challenged by results of the NORTH-C trial [12]. Using PEG-IFN alfa-2b 1.5 ug/kg/wk and RBV 800–1400 mg daily in patients (n = 298) with genotype 2 and 3, the authors were unable to show non-inferiority of the 14-week regimen (as compared to a 24-week regimen) in patients with RVR, with lower SVR (81% *vs.* 91%) and higher relapse rates (11% *vs.* 5%) in those treated for 14 weeks. Despite the inferiority of the 14-week regimen, Dalgard *et al.* suggested that a 26–32% reduction of drug exposure and cost with 14 weeks of treatment in patients with RVR – recognizing that this would entail a 24-week course of retreatment for the minority with relapse – justified truncation of therapy in such patients (as long as the relapse rate is less than 35%) [12].

Given the intense motivation among most physicians and patients to optimize the chance of success with the initial course of therapy for CHC, the non-uniformity of the data on truncation of therapy in patients with genotypes 2 and 3 who attain RVR has led many clinicians to continue to treat these patients for 24 weeks. The study by Manns *et al.* [15], as reported in the current issue of the Journal, provides the opportunity to glean further insights into this question, along with other aspects of therapy for patients with genotypes 2 and 3, within the context of a large study evaluating both a lower dose of PEG-IFN alfa-2b and a reduced treatment duration. In this study, treatment-naïve patients with CHC genotype 2 and 3 infection were derived from two cohorts: the Hep-Net cohort enrolled in Germany and an international cohort enrolled throughout Europe and Asia. Patients were randomized to receive PEG-IFN alfa-2b (1.5 μg/kg/wk) for 24 weeks (group A), PEG-IFN alfa-2b (1.0 μg/kg/wk)

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for 24 weeks (group B) or PEG-IFN alfa-2b (1.5 μg/kg/wk) for 16 weeks (group C); all in combination with weight-based RBV (800–1200 mg/day). Treatment duration in group C, as well as in groups A and B, was independent of RVR; patients were not randomized to 16 *vs.* 24 weeks of therapy based on RVR. Moreover, data on week 4 HCV RNA were assessed only in the International cohort.

Of the 682 patients enrolled in the study 80% were of genotype 3, which potentially constrains the ability to draw comparably robust conclusions about both of the evaluated genotypes. SVR rates were 66.5%, 64.3%, and 56.6% for groups A, B, and C, respectively, with groups B and C failing to show non-inferiority relative to group A. Relapse rates were 17.8%, 16.3%, and 29.3%, respectively. Among those who achieved an RVR in the International cohort, SVR rates were consistently high across all treatment arms: 75.3%, 75.9%, and 72.4%, respectively. The relapse rates in the RVR patients were not provided. Among genotype 3 patients, SVR was similar in groups A and B but lower in group C. While in group A SVR rates were highest in patients with genotype 2 infection and low baseline viral load, even among genotype 2 patients with low baseline viral load, SVR rates were lower in group C compared with group A. Treatment-related serious adverse events were highest in group A and predictably, lowest in group C. However, adverse events leading to discontinuation of therapy were similar across the arms.

The current study by Manns *et al.* [15] adds support to the growing body of literature, including two recent meta-analyses [16,17], suggesting that 24 weeks of therapy should remain the standard of care for genotype 2 and 3 patients. It does demonstrate, however, that the dose of Peg-IFN alfa-2b can be reduced to 1.0 μg/kg/wk in those with safety concerns without substantial decline in efficacy. It reaffirms that genotype 3 patients should not be treated routinely for less than 24 weeks, as well as those patients with either genotype 2 and 3 without RVR. It again brings up the question whether, based on the low SVR rate of about 50% in these non-RVR populations, treatment of over 24 weeks duration might be indicated and randomized controlled trials, such as one currently in progress, are needed to address that issue.

While supporting 24 weeks as the overall standard of care, Manns *et al.* lend credence to the concept of truncation of therapy in patients with genotype 2 or 3 who achieve an RVR with weight-based ribavirin. The data in the overall literature, however, remain inconclusive as to whether this can be done routinely without jeopardizing the chance of SVR to any significant extent even among "favorable" patient populations with characteristics such as younger age [7,10,11,18], no or minimal fibrosis [7,9,11,19], BMI $\leqslant$30 kg/m^2 [11,19,20], low viral load [7–9,11,19], genotype 2 [8,11], or platelet count $\geqslant$140,000 [20]. Despite the potential merit of a cost-effectiveness argument in support of shorter treatment, or a modest improvement in tolerability, many clinicians would find it problematic to routinely administer a regimen that had failed to demonstrate non-inferiority to patients who wish to maximize their prospects of success during the initial treatment course without incurring any incremental chance of having to undergo a repeat therapy. Based on the available data, truncated therapy with PEG-IFN and RBV should be reserved – after individualized discussion about benefit-risk considerations – for genotype 2 or 3 patients with favorable treatment characteristics who have attained RVR if they have significant tolerability issues after 12–16 weeks of therapy.

Conflict of interest

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References

[1] Zeuzem S, Herrmann E, Lee JH, et al. Viral kinetics in patients with chronic hepatitis C treated with standard or peginterferon alpha-2a. Gastroenterol 2001;120:1438–1447.
[2] Neumann AU, Lam NP, Dahari H, et al. Differences in viral dynamics between genotypes 1 and 2 of hepatitis C virus. J Infect Dis 2000;182:28–35.
[3] Mangia A, Santoro R, Minerva N, et al. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. N Engl J Med 2005;352:2609–2617.
[4] Dalgard O, Mangia A. Short-term therapy for patients with hepatitis C virus genotype 2 or 3 infection. Drugs 2006;66:1807–1815.
[5] Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trail. Lancet 2001;358:958–965.
[6] Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronci hepatitis C virus infection. N Engl J Med 2002;347:975–982.
[7] Dalgard O, Bjoro K, Hellum KB, et al. Treatment with pegylated interferon and ribavirin in HCV infection with genotype 2 or 3 for 14 weeks: a pilot study. Hepatology 2004;40:1260–1265.
[8] VonWagner M, Huber M, Berg T, et al. Peginterferon alfa-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. Gastroenterol 2005;120:1438–1447.
[9] Mecenate F, Pellicelli AM, Barbaro G, et al. Short versus standard treatment with pegylated interferon alfa-2A plus ribavirin in patients with hepatitis C virus genotype 2 or 3: the CLEO trial. BMC Gastroenterol 2010;19:10–21.
[10] Yu ML, Dai CY, Huang JF, et al. A randomized study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. Gut 2007;56:553–559.
[11] Shiffman ML, Suter F, Bacon BR, et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. N Engl J Med 2007;357:124–134.
[12] Dalgard O, Bjoro K, Ring-Larsen H, et al. Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virologic response. Hepatology 2008;47:35–43.
[13] Zeuzem S, Hultcrantz R, Bourliere M, et al. Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. J Hepatol 2004;40:993–999.
[14] Hadziyannis SJ, Sette Jr H, Morgan TR, et al. Peginterferon-α2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004;140:346–355.
[15] Manns MP, Zeuzem S, Sood A, et al. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. J Hepatol 2011;55:554–563.
[16] Andriulli A, Mangia A, Iacobellis A, et al. Meta-analysis: the outcome of antiviral therapy in HCV genotype 2 and 3 infected patients with chronic hepatitis. Aliment Pharmacol Ther 2008;28:397–404.
[17] Slavenburg S, Weggelaar I, van Oijen MG, et al. Optimal length of antiviral therapy in patients with hepatitis C virus genotype 2 and 3: a meta-analysis. Antivir Ther 2009;14:1139–1148.
[18] Lagging M, Langeland N, et al. NORDynamIC Study Group. Randomized comparison of 12 or 24 weeks of peginterferon alfa-2a and ribavirin in chronic hepatitis C virus genotype 2/3 infection. Hepatology 2008;47:1837–1845.
[19] Diago M, Shiffman ML, Bronowicki JP, et al. Identifying hepatitis C virus genotype 2/3 patients who can receive a 16-week abbreviated course of peginterferon alfa-2a (40 KD) plus ribivirin. Hepatology 2010;51:1897–1903.
[20] Mangia A, Minerva N, Bacca D, et al. Determinants of relapse after a short (12 weeks) course of antiviral therapy and re-treatment efficacy of a prolonged course in patients with chronic hepatitis C virus genotype 2 or 3 infection. Hepatology 2009;49:358–363.